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Mechanisms of antibiotic resistance

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Antibiotics represent one of the most successful forms of therapy in medicine. But the efficiency of antibiotics is compromised by a growing number of antibiotic-resistant pathogens. Antibiotic resistance, which is implicated in elevated morbidity and mortality rates as well as in the increased treatment costs, is considered to be one of the major global public health threats (www.who.int/drugresistance/en/) and the magnitude of the problem recently prompted a number of international and national bodies to take actions to protect the public (http://ec.europa.eu/dgs/health_consumer/docs/road-map-amr_en.pdf; http://www.who.int/drugresistance/amr_global_action_plan/en/; http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf). Understanding the mechanisms by which bacteria successfully defend themselves against the antibiotic assault represent the main theme of this eBook published as a Research Topic in *Frontiers in Microbiology: Antimicrobials, Resistance, and Chemotherapy*. The articles in the eBook update the reader on various aspects and mechanisms of antibiotic resistance. A better understanding of these mechanisms should facilitate the development of means to potentiate the efficacy and increase the lifespan of antibiotics while minimizing the emergence of antibiotic resistance.

The multidrug efflux systems contribute significantly to the increased resistance to multiple antibiotics in bacteria. A major challenge in developing efficacious antibiotics against drug-resistant pathogens is to identify compounds that can counteract the efflux functions. The wealth of bacterial genomics information available suggests the presence of a variety of efflux systems in bacteria. Even a single bacterium may possess multiple efflux transporters of different families, with the overlapping substrate spectra. Accumulating evidence has indicated that the MexXY multidrug efflux system is a primary determinant of aminoglycoside resistance in *Pseudomonas aeruginosa*. Morita et al. (2012) provided a timely review on the *P. aeruginosa* MexXY pump and other aminoglycoside efflux pumps in a range of different bacteria. The expression of bacterial multidrug efflux system is usually controlled by transcriptional regulators that either repress or activate the transcription of the multidrug efflux genes. The articles

by Usui et al. (2013) and Deng et al. (2013) further illustrated the complexity of regulation of multidrug efflux systems. However, the importance of multidrug efflux system may not be overstated for a specific antibiotic or organism, which is supported by the findings of Baucheron et al. (2014).

β -lactam antibiotics, which inhibit the biosynthesis of bacterial cell wall, are the most widely available antibiotics used to treat a number of bacterial infections. Resistance to β -lactam antibiotics, however, has become a worldwide health care problem. Production of β -lactamases is a major and threatening resistance mechanism toward β -lactam antibiotics. Epidemiological work by Chuma et al. (2013) demonstrated a recent emergence of β -lactamase-mediated cefotaxime resistance in *Salmonella enterica* Serovar Infantis. To counteract β -lactam resistance in pathogenic bacteria, extensive research in the past three decades has focused on the discovery of novel compounds inhibiting the β -lactamase function. Watkins et al. (2013) reviewed the novel β -lactamase inhibitors that are close to being introduced in the clinical practice. Despite the successful development of β -lactamase inhibitors for the combination therapy, the use of β -lactamase inhibitors is still challenged by the variable affinity of inhibitors to different β -lactamases and by the vast quantity of β -lactamases produced by the resistant strains. To address this issue and optimize the existing β -lactam-based therapy, Zeng and Lin (2013) proposed to inhibit the induction of β -lactamases by targeting the key players required for β -lactamase induction, such as lytic transglycosylase.

Aminoglycosides are another class of clinically important antibiotics for treating various bacterial pathogens. The increasing resistance of clinical isolates against aminoglycosides, however, has compromised the effectiveness of this class of antibiotics. A major mechanism of aminoglycoside resistance is the production of aminoglycoside-modifying enzymes. Two enzymes with aminoglycoside-modifying activities are discussed in this research topic. Shi et al. (2013) provided a comprehensive overview of the structure of aminoglycoside kinase and reported on the recent progress in the discovery of aminoglycoside phosphotransferase inhibitors using structure-guided strategies. Aminoglycoside 6'-N-acetyltransferase type Ib is another clinically important

enzyme prevalent in a wide variety of Gram-negative pathogens. Ramirez et al. (2013) reviewed the unique sequence, genomics and functional features of this type of aminoglycoside-modifying enzymes. They also provided an insightful discussion on the development of innovative antisense technologies to combat this type of aminoglycoside resistance.

Several articles are focused on the discovery of innovative antimicrobials by harnessing our knowledge in bacterial physiology and pathogenesis. Quorum sensing is a unique cell-to-cell communication that modulates the expression of antibiotic resistance as well as virulence genes. Thus, the key compounds mediating quorum sensing such as acylated homoserine lactone have been attractive targets for antimicrobial chemotherapy. Hirakawa and Tomita (2013) reviewed recent progress in the discovery of acylated homoserine lactone inhibitors/modulators and discussed the feasibility of targeting other molecular components involved in signal transduction (e.g., regulatory elements) to modulate quorum sensing. Olivares et al. (2013) provided a timely review to analyze recent works on the intrinsic resistome, that is the concerted activity of elements required for the intrinsic resistance in *E. coli* and *P. aeruginosa*. The feasibility of using intrinsic resistome inhibitors for potentiating the effects of clinical drugs is also discussed in this review. Iino et al. (2013) used a large-scale femtoliter droplet array for single-cell analysis to assess the heterogeneity among the individual cells, enabling the identification of the novel or unconventional mechanisms of antibiotic resistance or resistance against novel antibiotics.

This research topic also includes a panel of articles focused on specific resistance mechanisms in different pathogens. Tuberculosis (TB) is notoriously known for its resistance to multiple drugs. Green and Garneau-Tsodikova (2013) focused on various mechanisms of resistance to the currently available anti-TB drugs and provided perspectives for novel strategies and lead scaffolds/compounds that are aimed at deterring these resistance mechanisms. In an effort to reduce emerging resistance, combinations of small molecules and a high-throughput synergy screening have been also explored (Zhang et al., 2007). Ilina et al. (2013) observed that a mutation in the ribosomal protein S5 is responsible for the resistance of *Neisseria gonorrhoeae* strains against multiple drugs including the decreased susceptibility to spectinomycin, cefixime and ceftriaxone. Zaheer et al. (2013) found that both therapeutic and subtherapeutic macrolide administration significantly increased the proportion of erythromycin resistant enterococci but had no effect on the development of macrolide resistance in *Mannheimia haemolytica*, both isolated from the nasopharynx. Sun et al. (2013) reported that sterol C-22 desaturase ERG5, which is highly conserved among various fungal species, is involved in azole resistance and may serve as a novel target for antifungal drugs, in particular against *Neurospora crassa* and *Fusarium verticillioides*. Using the population-based multivariate analysis, Abbes et al. (2013) observed that fluconazole resistance in *Candida glabrata* involves complex interactions between drug resistance gene expression and/or copy number.

Recent metagenomics and functional genomics studies have provided a compelling evidence that antibiotic resistance genes are widespread and the natural reservoirs of potential antibiotic resistance include many ecosystems such as in agriculture

(e.g., animal manure, soil, water, wastewater lagoons), the gut of humans and food animals, and even ancient soils. The diverse range of novel antibiotic resistance genes could be accessible to clinically relevant bacteria and play a critical role in the emergence of antibiotic resistance among pathogens. Pehrsson et al. (2013) provided an insightful review for the novel resistance functions uncovered using the functional metagenomic examination of various resistance reservoirs. Municipal biosolids that are produced during the activated sludge treatment are also a significant reservoir of antibiotic resistance as assessed by Kaplan et al. (2013). Burch et al. (2013) explored an alternative approach, aerobic digestion, to reduce the quantity of antibiotic resistance genes in wastewater solids. The occurrence of antibiotics resistance genes in finfish aquaculture environments is further discussed by Miranda et al. (2013). The presence of antibiotic resistance genes in the aquatic environment is also demonstrated by Fahrenfeld et al. (2013) and Suzuki et al. (2013). To address the key issue concerning the role of environmental resistance gene reservoir in the emergence of clinically important resistant pathogens, Perry and Wright (2013) reviewed recent works suggesting genetic exchange between the environmental and clinical resistomes. Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major cause of disease in the general population. Roberts et al. (2013) examined 55 environmental MRSA isolates from 805 samples and found that 98% of them are also resistant to other classes of antibiotics in addition to methicillin, thus most likely representing the antibiotic resistance gene pool in the environment. Clearly, with the aid of high-throughput sequencing and metagenomics approaches, recent studies of natural antibiotic resistance gene reservoirs have revealed a much higher level of diversity and novelty than anticipated. However, there is still a significant knowledge gap regarding the mechanisms of horizontal gene transfer that are involved in the exchange of genes among different ecological compartments. A better understanding of these *in situ* processes is required in order to control the development, transmission, and evolution of antibiotic resistant genes.

In summary, the articles within this eBook address various timely issues related to antibiotic resistance mechanisms. Clearly, discovery of new antimicrobials as well as finding strategies to expand the useful life of existing antibiotics is important to combat the ever-increasing antimicrobial resistance. Bacteria, however, possess an enormous diversity of genes that allow them, sooner or later, to counteract the action of newly invented antibiotics. As reflected in many articles in this eBook, the natural resistomes are common and exist in diverse environmental niches. Misuse of antibiotics, in terms of application and dosage, is an additional contributing factor for the development of antibiotic resistance (Nosanchuk et al., 2014). Consequently, to mitigate antibiotic resistance, we should cautiously use antibiotics from a One Health perspective (<http://www.onehealthinitiative.com/>). On the other hand, as it is also reflected in this Research Topic, in parallel to the development of new of antibiotics, it is imperative to study the molecular basis of resistance development so that we can prevent and overcome antibiotic resistance by targeting resistance mechanisms, which will make the existing and novel antibiotics more effective and sustainable.

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